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OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: March 28, 2011

SUBJECT: Penflufen: Report of the Cancer Assessment Review Committee

PC Code: 100249
Decision No.: N/A
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FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509P)

THROUGH: Jess Rowland, Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Linda Taylor, Toxicologist
RAB VII, Health Effects Division (7509P)

Marianne Lewis
IRB, RD (7505P)

The Cancer Assessment Review Committee met on February 16, 2011 to evaluate the cancer classification of Penflufen in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

PENFLUFEN

PC Code 100249

FINAL
March 28, 2011

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: Linda Taylor, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Lori Brunsman, Statistician

Marion Copley

Kit Farwell

Ray Kent

Karlyn Middleton

Esther Rinde — Retired

Jess Rowland, Chair

P.V. Shah

Yin-Tak Woo

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist

OTHER ATTENDEES: PMRA Canada (on phone): Carmen Chung, Ally Pen; Sadaf Shaukat (BPPD), Mike Metzger (HED), Donna Davis (HED)

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EXECUTIVE SUMMARY

On February 16, 2011, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of Penflufen.

Linda Taylor of Risk Assessment Branch VII presented the chronic toxicity/carcinogenicity study in Wistar Rats and the carcinogenicity study in C57BL/CJ mice. In the chronic toxicity/carcinogenicity study (MRID 48023815), penflufen (BYF 14182) was administered *via* the diet to Wistar rats at 100, 2000 and 7000 ppm, corresponding to 0, 4.0, 79 and 288 mg/kg/day in males and 0, 5.6, 113 and 399 mg/kg/day in females over a 24-month treatment period (10 rats/sex/group designated for the interim sacrifice after 52 weeks, 10 rats/sex/group designated for the recovery group sacrificed after 65 weeks following 52 week of treated diet, and 13 weeks of untreated diet, and 60 rats/sex/group designated for the final sacrifice after 104 weeks). In a carcinogenicity study (MRID 48023814), penflufen (BYF 14182) was administered *via* the diet to C57BL/6J mice (60/sex/group) at dose levels of 0, 100, 1000 or 6000 ppm (equivalent to 0, 14.3, 146, and 880 mg/kg/day in males and 0, 18.4, 182, and 1101 mg/kg/day in females) for 52 weeks. After 52 weeks, 10 mice/sex/group allocated to the chronic phase of the study were necropsied at the scheduled interim sacrifice. The remaining 50 mice/sex/group, allocated to the carcinogenicity phase of the study, continued treatment until the scheduled final sacrifice of the study after at least 78 weeks of treatment. Mutagenicity data and structure activity relationship was also discussed.

The CARC considered the following for a weight-of-evidence determination of the carcinogenic potential of penflufen.

Carcinogenicity

Rat

• *Hemolyphoreticular Tumors:* Male Wistar rats had a statistically significant trend, and a significant pair-wise comparison of the 7000 ppm dose group with the controls, for histiocytic sarcomas, both at $p < 0.05$. The historical control incidence of histiocytic sarcoma from the testing lab in male Wistar Rj:WI(IOPS HAN) rats ranged from 0 to 3.3%, with a mean of 0.8%. The concurrent control value was within the historical control range, while the tumors seen at the high dose (9%) exceeded the historical control range (0-3.3%). The CARC considered the histiocytic sarcomas to be treatment-related in male rats.

• *Brain Astrocytomas:* While there were no statistically significant differences in the incidence of brain astrocytomas in male rats, these were fatal tumors. The astrocytomas in the 7000 ppm male rats appeared in unscheduled sacrifice rats dying on test days 429, 520, and 687, with no concomitant increase in terminal sacrifice rats. The astrocytomas in the control and 100 ppm males were found at the scheduled sacrifice (day 733). The incidences in the control and 100 ppm groups (both 2%) were within the historical control range (0- 3.7%), but the incidence at 7000 ppm (5%) was outside the historical control range of 0-3.8%. The CARC considered the brain

astrocytomas to be treatment-related in male rats despite the lack of statistical significance and the small tumor increase, since brain astrocytomas are considered to be rare and were fatal tumors.

• *Ovarian tubulostromal Tumors:* Female rats had statistically significant trends in ovarian tubulostromal adenomas at $p<0.01$ and in ovarian tubulostromal combined adenomas and/or adenocarcinomas at $p<0.05$. There were no statistically significant pair-wise comparisons of the dosed groups with the controls. The incidence of adenomas at the high dose exceeded the historical control range (0-6.7%) of the laboratory. The CARC considered the ovarian tumors to be treatment-related in female rats.

• *Adequacy of Dosing:* Dosing at the 7000 ppm (288/399 mg/kg/day, M/F) is considered adequate in both male and female rats due to the presence of treatment-related tumors.

Mouse

• There were no treatment-related increases in tumors in either male or female mice.

• *Adequacy of Dosing:* Dosing at the high dose of 6000 ppm (880/1101 mg/kg/day, M/F) was considered to be adequate in both sexes of mice since it was close to the limit dose in males and exceeded the limit dose in females. The effects seen at the high dose were considered to be adaptive and not adverse, and there was no evidence of tumors.

Mutagenicity: There is no concern for mutagenicity.

Structure Activity Relationship: No structural alerts were identified.

Classification and Quantification of Carcinogenic Potential

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified penflufen as "Suggestive Evidence of Carcinogenic Potential." This classification was based on the presence of a statistically significant increase in histiocytic sarcomas (significant trend and pair-wise comparison of high dose group with controls) in male rats, but in the absence of a dose response and a lack of pre-neoplastic lesions. In addition, a marginal increase in brain astrocytomas, a fatal tumor, was also observed in male rats at the high dose, however, this effect was not dose-related and did not reach statistical significance (i.e., there was no trend or pair-wise significance). In addition, there were no pre-neoplastic lesion such as glial proliferation which is a good indicator of chemical tumor induction (i.e, there will be changes in the cells prior to transformation to a neoplasm). The ovarian adenomas observed at the high dose also showed no dose response, no pair-wise significance, no decrease in latency, and there were no pre-neoplastic lesions such as hyperplasia of the epithelial cells of the endometrium. Additionally, there was no evidence of carcinogenicity in male or female mice (at doses that were judged to be adequate to assess the carcinogenic potential), no concern for mutagenicity (*in vivo* or *in vitro*) for the parent molecule or the two metabolites, and there were no other lines of evidence (such as structure-activity relationship). Although these three tumors were considered treatment-related and raised a concern, they provided weak evidence of carcinogenicity (i.e. marginal tumor responses), and, therefore, a stronger conclusion for

carcinogenic potential could not be supported. Thus, the weight of evidence is suggestive of carcinogenic potential for penflufen.

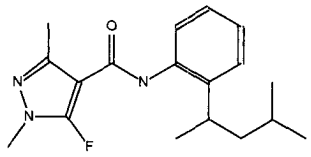
The evidence from animal data is suggestive of carcinogenicity which raises a concern for carcinogenic effects but is judged not sufficient for quantification of cancer risk in humans. Also, according the *Guidelines,* when there is a "Suggestive" classification, the Agency does not attempt a dose-response assessment as the nature of the data generally would not support one. Therefore, the Agency has determined that quantification of risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to penflufen.

I. INTRODUCTION

On February 16, 2011, the Cancer Assessment Review Committee of the Health Effects Division of the
Office of Pesticide Programs met to evaluate the carcinogenic potential of Penflufen.

II. BACKGROUND INFORMATION

Penflufen is a new active ingredient (broad spectrum fungicide), proposed for seed treatment to numerous crops. The PC Code is 100249, and the CAS number is 494793-67-8. This chemical is part of a global review, and the U.S. is the primary reviewer for the toxicology data. The structure of penflufen is presented below.



PENFLUFEN

The liver is the primary target organ in all species tested and following all durations of exposure. The principle effects include increased liver weight, centrilobular hepatocyte hypertrophy, with or without relevant clinical chemistry parameters. The hepatic total cytochrome P-450 content and BROD and PROD related activities were shown to be increased in both sexes following subchronic oral exposure. The thyroid is also a target organ (increased thyroid weight, thyroid follicular cell hypertrophy/hyperplasia).

III. EVALUATION OF CARCINOGENICITY STUDIES

1. *Combined Chronic Toxicity/Carcinogenicity Study in Rats*

Reference: Chronic Toxicity and Carcinogenicity Study of BYF 14182 in the Wistar Rat by Dietary Administration. (2009). Study No. SA 061150, Document No. M-357848-01-2. November 27, 2009. MRID 48023815.

A. Experimental Design: BYF 14182, (Batch No. 2005-004498, 95.6% purity) was administered *via* the diet to Wistar rats at 100, 2000 and 7000 ppm, corresponding to 0, 4.0, 79 and 288 mg/kg/day in males and 0, 5.6, 113 and 399 mg/kg/day in females over a 24-month treatment period (10 rats/sex/group designated for the interim sacrifice after 52 weeks, 10 rats/sex/group designated for the recovery group sacrificed after 65 weeks following 52 week of treated diet, and 13 weeks of untreated diet, and 60 rats/sex/group designated for the final sacrifice after 104 weeks).

Survival Analyses: There were no survival disparities among the dose groups for male rats (Brunsman, L., 01/27/2011, TXR No. 0055636).

Table 1. Penflufen – Wistar Rat Study (MRID 48023815)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	53[i]	53-78	79-107[f]	Total
0	0/70	0/70	10/70	11/60	30/49	41/60 (68)
100	0/70	1/70	10/69	13/59	22/46	36/60 (60)
2000	0/70	1/69[a]	9/68	9/57[b]	26/47[c]	36/57 (63)
7000	0/70	2/70	10/68	11/58	21/45[d]	34/58 (59)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.
[f]Final sacrifice at weeks 105-107.

( )Percent.

[a]One accidental death at week 42, dose 2000 ppm.
[b]One accidental death each at weeks 53 and 78, dose 2000 ppm.
[c]One accidental death at week 104, dose 2000 ppm.
[d]One accidental death each at weeks 90 and 104, dose 7000 ppm.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Female rats had statistically significant negative pair-wise comparison of the 2000 ppm and 7000 ppm dose groups with the controls, both at $p<0.05$ (Brunsman, L., 01/27/2011, TXR No. 0055636).

Table 2. Penflufen – Wistar Rat Study (MRID 48023815)

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-52	53[i]	53-78	79-107[f]	Total
0[#]	1/70[a]	1/68[b]	10/67	6/57	21/50[c]	29/58 (50)
100	0/70	0/70	10/70	7/60	15/52[d]	22/59 (37)
2000	1/70	1/69	10/68	2/58	13/56	17/60 (28)[*n]
7000	1/70	2/69	9/67	4/58	11/54	18/61 (30)[*n]

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.
[#]There were 71 animals in the carcinogenicity phase of the control group. There were 70 animals in all other dose groups.
[i]Interim sacrifice at week 53.
[f]Final sacrifice at weeks 105-107.
( )Percent.

[n]Negative change from control
[a]One accidental death at week 14, dose 0 ppm.
[b]One accidental death at week 52, dose 0 ppm.
[c]One accidental death at week 104, dose 0 ppm.
[d]One accidental death at week 103, dose 100 ppm.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

B. Discussion of Tumor Data:

(1) Hemolymphoreticular Tumors[1]: Male rats had a statistically significant trend, and a significant pair-wise comparison of the 7000 ppm dose group with the controls, for histiocytic sarcomas, both at $p < 0.05$ (Brunsman, L, 01/27/2011, TXR No. 0055636). Subsequent to the CARC meeting, Bayer CropScience provided historical control data for histiocytic sarcomas from the testing facility that conducted the combined chronic/carcinogenicity study in rats (initiated in December, 2006). The historical control data are from nine studies performed from December 2000 to January 2006. The historical control incidence of histiocytic sarcoma in male Wistar Rj:WI(IOPS HAN) rats ranged from 0 to 3.3%, with a mean of 0.8%. The concurrent control value was within the historical control range, while the tumors seen at the high dose (9%) exceeded the historical control range (0-3.3%).

Table 3. Penflufen – Wistar Rat Study (MRID 48023815)

Male Hemolymphoreticular Tumor Rates[+]
and Fisher's Exact Test and Exact Trend Test Results

	Dose (ppm)			
	0	100	2000	7000
Histiocytic Sarcomas (%)	0/60 (0)	3/59 (5)	3/58 (5)	5[a]/58 (9)
p =	0.03783*	0.11872	0.11560	0.02619*

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.
[a]First sarcoma observed at week 77, dose 7000 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

(2) Brain astrocytomas. There are no statistically significant differences in the incidence of brain astrocytomas (Table 4). The astrocytomas in the 7000 ppm male rats appeared in unscheduled sacrifice rats dying on test days 429, 520, and 687, with no concomitant increase in terminal sacrifice rats. The brain astrocytomas in the control and 100 ppm males were found at the scheduled sacrifice (day 733). The historical control data are from ten studies performed at the testing facility from December 2000 to January 2006. The incidence of astrocytoma in male Wistar Rj:WI(IOPS HAN) rats ranged from 0 to 3.7%, with a mean of 1.5%. The incidences in the control and 100 ppm groups (both 2%) were within the historical control range (0- 3.7%), but

[1] The histiocytic sarcomas were under the heading of hematopoietic tumors in the study. However, the more correct terminology for this type of tumor is "hemolymphoreticular" tumors.

the incidence at 7000 ppm (5%) was outside the historical control range of 0-3.8%. The time of first occurrence of these astrocytomas in the historical control was not provided.

Table 4. Penflufen – Wistar Rat Study (MRID 48023815)

Male Brain Astrocytoma Tumor Rates[+]
and Fisher's Exact Test and Exact Trend Test Results

	Dose (ppm)			
	0	100	2000	7000
Astrocytomas (%)	1/60 (2)	1/59 (2)	0/57 (0)	3[a]/58 (5)
p =	0.08925	0.74790	1.00000	0.29654

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.

[a]First astrocytoma observed at week 63, dose 7000 ppm.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

(3) Ovarian tubulostromal tumors: Female rats had statistically significant trends in ovarian tubulostromal adenomas at $p<0.01$ and in ovarian tubulostromal combined adenomas and/or adenocarcinomas at $p<0.05$. There were no statistically significant pair-wise comparisons of the dosed groups with the controls. The statistical analyses of the tumors in the female rats were based upon Peto's Prevalence Test due to survival disparities among the dose groups (Brunsman, L, 01/27/2011, TXR No. 0055636). Subsequent to the CARC meeting, Bayer CropScience provided historical control data for tubulostromal adenomas (0-6.7%) and adenocarcinomas (0%) in the ovary from the testing facility that conducted the combined chronic/carcinogenicity study in rats (initiated in December, 2006). The historical control data are from ten studies performed from December 2000 to January 2006.

Table 5. Penflufen – Wistar Rat Study (MRID 48023815)

Female Ovarian Tumor Rates[+] and
Peto's Prevalence Test Results

	Dose (ppm)			
	0	100	2000	7000
Adenomas[a] (%)	2/29 (7)	1/37 (3)	1/43 (2)	7/43 (16)
p =	0.00697**	0.78977	0.82776	0.12051
Adenocarcinomas[a] (%)	0/29 (0)	1/37 (3)	1/43 (2)	0/43 (0)
p =	0.77181	0.18799	0.20576	-
Combined (%)	2/29 (7)	2/37 (5)	2/43 (5)	7/43 (16)
p =	0.02415*	0.59873	0.65730	0.12051

+ Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]All adenomas and adenocarcinomas observed at final sacrifice, simultaneously in all dose groups.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

C. Non-neoplastic lesions: Ovary: The incidences of tubulostromal hyperplasia both in the concurrent control and the treated groups (Table 6) were within the historical control range (0-25%) of the testing laboratory.

Table 6: Incidence and severity of tubulostromal hyperplasia in the ovary-all rats

Sex	Females			
BYF 14182 Dose level (ppm)	**0**	**100**	**2000**	**7000**
Number examined	**60**	**60**	**60**	**59**
Tubulostromal hyperplasia: focal				
Minimal	2	0	0	5
Slight	0	2	0	0
Moderate	0	2	0	1
Marked	1	0	1	1
Total	**3 (5%)**	**4 (6.7%)**	**1 (1.7%)**	**7 (11.9%)**

Liver: There was a dose-related increase in the incidence of centrilobular to panlobular hepatocellular hypertrophy and of centrilobular hepatocellular macrovacuolation in both sexes, and females displayed a higher incidence of hepatocellular brown pigments (Table 7).

Table 7. Incidence and severity of microscopic changes in the liver (rat chronic toxicity/carcinogenicity study)

Sex	Males				Females			
BYF 14182 Dose level (ppm)	**0**	**100**	**2000**	**7000**	**0**	**100**	**2000**	**7000**
Number of examined animals	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Hepatocellular hypertrophy: centrilobular to panlobular								
Minimal	0	5	20	39	0	0	21	26
Slight	0	0	1	11	0	0	1	20
Moderate	0	0	0	0	0	0	0	1
Total	0	5*	21**	50**	0	0	22**	47**
Hepatocellular macrovacuolation: mainly centrilobular: diffuse								
Minimal	0	1	8	21	0	0	13	19
Slight	0	0	1	2	0	0	3	8
Moderate	0	0	0	0	0	0	2	2
Marked	0	0	0	0	0	0	0	1
Total	0	1	9**	23**	0	0	18**	30**
Hepatocellular brown pigment: focal								
Minimal	0	0	0	2	1	0	8	9
Slight	0	0	0	0	0	0	1	2
Total	0	0	0	2	1	0	9*	11**
Hepatocellular vacuolation: mainly periportal: diffuse								
Minimal	2	9	2	2	15	14	12	7
Slight	3	0	5	3	16	13	12	3
Moderate	3	3	0	1	5	4	2	0
Marked	0	2	0	1	0	1	1	0
Total	8	14	7	7	36	32	27	10
Eosinophilic focus(i) of hepatocellular alteration								
Minimal	22	26	26	20	25	24	23	23
Slight	1	4	6	9	2	14	22	15
Moderate	0	0	0	1	0	0	1	1
Total	23	30	32	30	27	38	46**	39*

** $p \leq 0.01$; * $p \leq 0.05$: only increased incidences were analyzed statistically (adjusted for survival)

D. Adequacy of the Dosing for Assessment of Carcinogenicity

Dosing at the 7000 ppm (288/399 mg/kg/day, M/F) is considered adequate in both male and female rats due to the presence of treatment-related tumors.

The findings at 7000 ppm, which included decreased body weight/body weight gain in females, increased liver weight in both sexes, increased incidence of centrilobular to panlobular hepatocellular hypertrophy and of centrilobular hepatocellular macrovacuolation in both sexes, increased incidence of hepatocellular brown pigment in females, colloid alteration in the thyroid in females, and increased cholesterol in females, were considered to be an adaptive response and not adverse. The results of the subchronic studies, which were also considered adaptive, suggest that the limit dose (20,000 ppm) would have been tolerated. However, due to the presence of treatment-related brain astrocytomas and histiocytic sarcomas in males and ovarian tumors in females, the high dose is considered to be adequate.

2. Carcinogenicity Study in Mice

Reference: Carcinogenicity study of BYF 14182 in the C57BL/6J mouse by dietary administration (2009). Study No. *SA* 06326; Document No. M-357859-01-2. October 23, 2009. MRID 48023814.

A. Experimental Design: In a carcinogenicity study (MRID 48023814), BYF 14182 (Batch No. 2005-004498, 95.6% purity) was administered *via* the diet to C57BL/6J mice (60/sex/group) at dose levels of 0, 100, 1000 or 6000 ppm (equivalent to 0, 14.3, 146, and 880 mg/kg/day in males and 0, 18.4, 182, and 1101 mg/kg/day in females) for 52 weeks. After 52 weeks, 10 mice/sex/group allocated to the chronic phase of the study were necropsied at the scheduled interim sacrifice. The remaining 50 mice/sex/group, allocated to the carcinogenicity phase of the study, continued treatment until the scheduled final sacrifice of the study after at least 78 weeks of treatment.

B. Discussion of Tumor Data: Exposure of mice to BYF 14182 at dose levels greater than or near the limit dose for a period of 78 weeks did not result in an increase in the incidence of any tumor type in either sex.

C. *Non-neoplastic findings*: A higher incidence and/or severity of diffuse centrilobular hepatocellular hypertrophy were observed in both sexes at all dose levels (Table 8). These changes were found to be dose-related. At 1000 and 6000 ppm, a higher severity of diffuse hepatocellular vacuolation was observed in females. At 6000 ppm, a higher incidence and severity of diffuse mainly periportal hepatocellular macrovacuolation were observed in females.

Table 8. Incidence and severity of microscopic changes in the mouse liver

Sex	Male				Female			
BYF 14182 dose level (ppm)	0	100	1000	6000	0	100	1000	6000
Number examined	48	49	49	48	50	50	50	50
Centrilobular hepatocellular hypertrophy: diffuse								
Minimal	0	9	17	2	0	2	4	20
Slight	0	3	9	15	0	1	1	10
Moderate	0	1	3	29	0	0	0	1
Total	0	13**	29**	46**	0	3	5*	31**
Hepatocellular vacuolation: diffuse								
Minimal	8	10	7	13	16	7	14	12
Slight	2	2	4	6	20	24	16	18
Moderate	0	0	1	0	2	9	14	14
Total	10	12	12	19*	38	40	44	44
Hepatocellular macrovacuolation: mainly periportal : diffuse								
Minimal	0	0	1	1	11	8	7	9
Slight	0	0	0	0	3	3	0	22
Moderate	0	0	0	0	0	0	0	10
Total	0	0	1	1	14	11	7	41**

* $p \leq 0.05$; **: $p \leq 0.01$

D. <u>Adequacy of the Dosing for Assessment of Carcinogenicity</u>:

Dosing at the high dose of 6000 ppm (880/1101 mg/kg/day, M/F) was considered to be adequate in both sexes of mice since it was the limit dose. The effects seen at the high dose were considered to be adaptive and not adverse, and there was no evidence of tumors.

No treatment-related mortality or clinical signs of toxicity were observed in either sex at any dose level. Slight decreases in overall BWG were observed in both sexes at 6000 ppm, but terminal body weights were comparable to the control (both sexes). Initial body weight gain was decreased in females at 6000 ppm (↓27%), and males at 6000 ppm displayed a reduced BWG over the first 6 weeks (↓18%). Liver weights were increased in both sexes at 6000 ppm, which is consistent with the finding of enlarged livers at necropsy. Treatment-related microscopic changes were seen in the liver (both sexes) and the thyroid gland (females). A higher incidence and severity of follicular cell hyperplasia in the thyroid gland were observed in females at 6000 ppm compared to the control females.

A Lowest Observed Adverse Effect Level (LOAEL) was not identified in this study, which included a dose level that exceeded the limit dose in females (1101 mg/kg/day) and one that was close to the limit dose in males (880 mg/kg/day). The liver effects and associated effects on the thyroid are considered adaptive and not adverse. In the subchronic oral toxicity study in mice at somewhat higher dose levels on a mg/kg/day bases (1238 mg/kg/day and 1600 mg/kg/day), a similar liver response was observed, indicating that continued exposure does not result in additional/more severe toxicity.

IV. TOXICOLOGY

1. Metabolism

The absorption, distribution, excretion and metabolism of Penflufen (BYF 14182) in rats were investigated using both the [phenyl-UL-$^{13}C_6$/^{14}C]- and [pyrazole-3-^{14}C]-labelled test compounds.

48023831	Bongartz, R.; Miebach, D. (2009) [Phenyl-UL-(Carbon 13)/(Carbon 14)]BYF 14182: Absorption, Distribution, Excretion and Metabolism in the Rat. Project Number: M/352042/01/2, MEF/08/175, M1824534/7. Unpublished
48023832	Bongartz, R.; Miebach, D. (2009) [Pyrazole-3-(Carbon 14)]BYF 14182: Absorption, Distribution, Excretion and Metabolism in the Rat. Project Number: M/348815/01/2, MEF/08/176, M1824533/6. Unpublished
48023833	Koester, J. (2009) Quantitative Whole Body Autoradiography of [Phenyl-UL-(Carbon 13)/(Carbon 14)]BYF 14182 in Male and Female Rats: Distribution of Radioactivity and Elimination from Blood, Organs and Tissues After Single Oral Administration Including Determination of Radioactivity in the Excreta and Exhaled ((Carbon 14) Carbon Dioxide). Project Number: M/345178/01/2, MEF/08/162, M1811491/5. Unpublished
48023834	Koester, J. (2009) Quantitative Whole Body Autoradiography of [Pyrazole-3-(Carbon 14)]BYF 14182 in Male and Female Rats: Distribution of Radioactivity and Elimination from Blood, Organs and Tissues After Single Oral Administration Including Determination of Radioactivity in the Excreta and Exhaled ((Carbon 14) Carbon Dioxide). Project Number: M/344803/01/2, MEF/08/179, M1811667/0. Unpublished
48023835	Koester, J. (2009) [Phenyl-UL-(Carbon 13)/(Carbon 14)]BYF 14182 - Metabolism in Organs and Tissues of Male and Female Rats (3 Time-Points). Project Number: M/354487/01/2, MEF/09/475, M1824542/6. Unpublished
48023836	Bongartz, R.; Miebach, D. (2009) [Pyrazole-3-(Carbon 14)]BCS-AA10006 (BYF 14182-3-Hydroxy-Butyl) - Absorption, Distribution, Excretion and Metabolism in the Rat. Project Number: M/354679/01/2, MEF/09/376, M1824556/1. Unpublished

The results with the two different labels are in good agreement with each other. The absorption of the radioactivity from the gastrointestinal tract (GIT) was rapid (within 40 to 90 minutes) and almost complete (94% of the dose in bile fistulation experiments). Excretion *via* bile was higher than the faecal excretion of non-bile fistulated rats. The renal excretion in bile fistulation experiments was correspondingly lower. No significant differences in the excretion pattern of radioactivity were observed between the two positions of radiolabel or between sexes. The results from the whole body autoradiography showed that the radioactivity was distributed among all tissues, and tissue concentrations were in the same order of magnitude irrespective of the label. Highest residues at the end of the study were observed in the blood, liver, and kidney. More than 93% of the administered radioactivity was excreted at study termination for both labels.

BYF 14182 was very extensively metabolised in the rat, and numerous metabolites were identified. Unchanged parent compound was found only in low percentages of the administered radioactivity. The metabolite pattern was identical in all studies for common metabolites and in good agreement for the label-specific metabolites. Metabolic reactions were detected in at least 10 different positions of the molecule. Because of the combination of transformations at these different sites, the large number of metabolites can be explained (see Figure 5.11-1). There were no different metabolites found in males and females, but the quantity of some metabolites seemed to differ with regard to sex (e.g. BYF 14182-desmethyl-dihydroxy-ketone: ≈ 5% for male and 17% for females). Most of the metabolites were demethylated in the pyrazole ring. Hydroxylation was another major metabolic reaction leading to trihydroxy and dihydroxy compounds. A minor part of the metabolites was hydroxylated in one position only. Further oxidation of hydroxy groups yielded ketones or carboxylic acids. Conjugation with glucuronic acid was only detected in higher amounts in the bile. Metabolites, originating from cleavage in the alkyl side chain with further oxidation, were found (≈ 6% of the dose). Label-specific metabolites containing only the pyrazole ring were quantitatively insignificant. A prominent hydroxylation reaction occurred in the 3 position of the alkyl side chain. The single metabolite BYF 14182-3-hydroxy-butyl was detected in very low amounts, only in the bile. However, many metabolites originating from BYF 14182-3-hydroxy-butyl were identified. Therefore, **BYF 14182-3-hydroxy-butyl was described as a key intermediate in the rat metabolism.** This assumption was supported by the findings of a separate rat ADME study with BYF 14182-3-hydroxy-butyl. In this study the same metabolic pattern was found as in the metabolism studies with the parent compound, demonstrating that the rat is systemically exposed to BYF 14182-3-hydroxy-butyl after administration of BYF 14182.

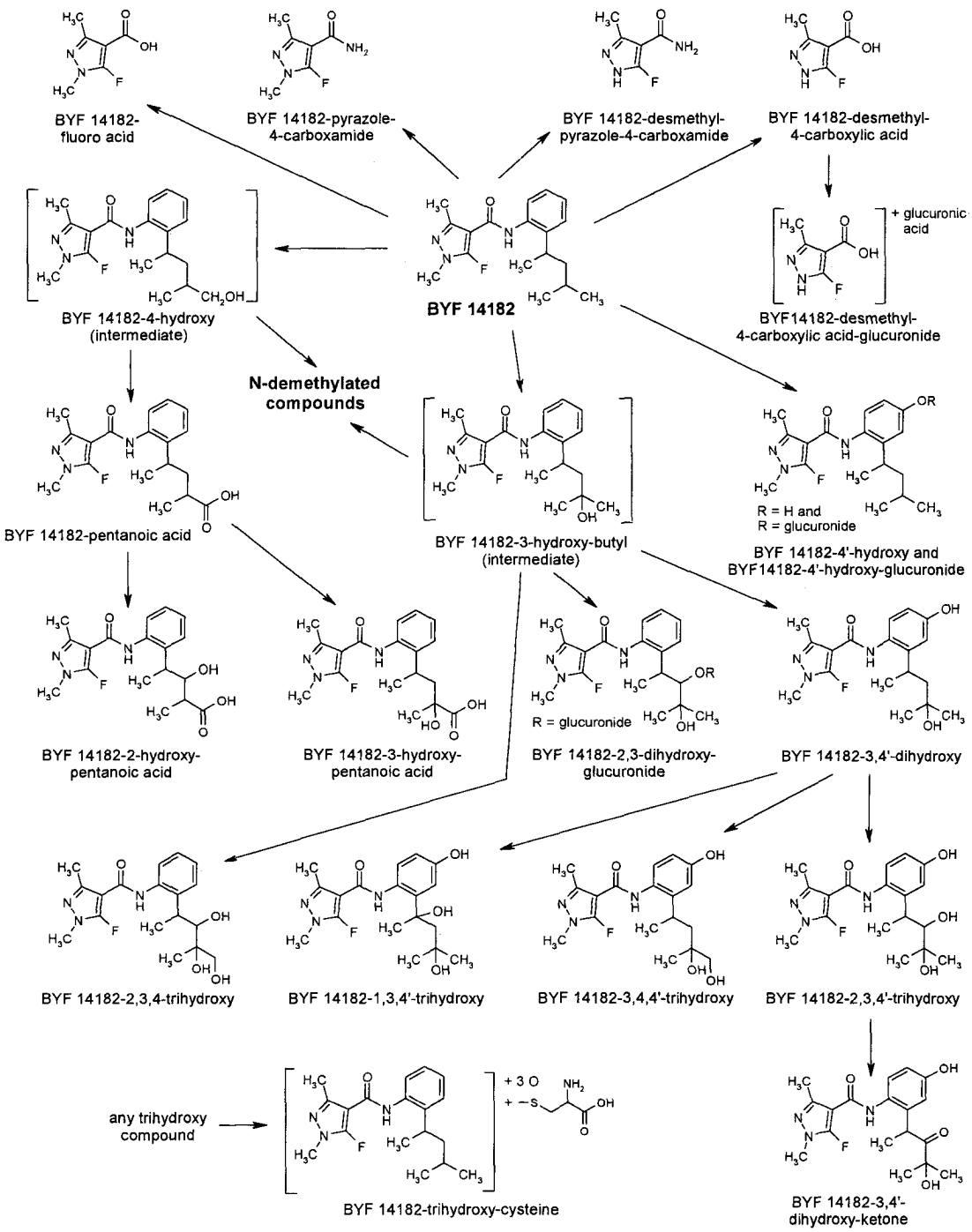
The principal metabolic reactions of BYF 14182 in the rat are:

- ▶N-demethylation in the pyrazole ring
- ▶hydroxylation at the following positions of the molecule: the alkyl side chain of the phenyl ring, the position 4' of the phenyl ring and the methyl group in position 3 of the pyrazole ring
- ▶further oxidation of the hydroxy group in the position 2 of the alkyl side chain forming a keto group
- ▶further oxidation of the hydroxy group in the position 4 of the alkyl side chain forming a carboxylic acid
- ▶oxidative cleavages of the alkyl side chain forming an acetyl group or a carboxylic acid group
- ▶conjugation of the hydroxy group in the position 4' of the phenyl ring and in the position 2 of the alkyl side chain with glucuronic acid
- ▶further oxidation of the hydroxymethyl group of the pyrazole ring forming a carboxylic acid group
- ▶conjugation of a trihydroxy compound with cysteine
- ▶cleavage of the carboxamide bond forming carboxylic acid, which was further metabolised via conjugation with glucuronic acid
- ▶cleavage of the N-phenyl bond forming the carboxamide

A proposed metabolic pathway for Penflufen (BYF 14182) in rats is shown in Figure 5.11-1.

Figure 5.11-1 Proposed metabolic pathway of BYF 14182 in rats

Part A

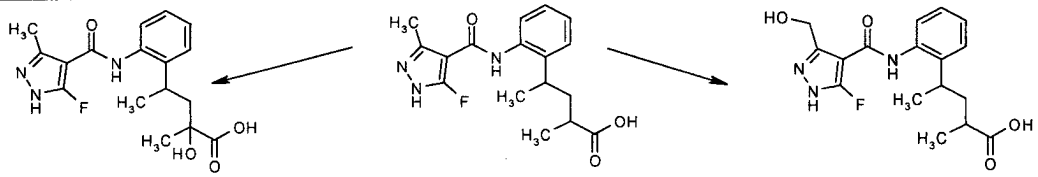


The pathway is continued on the next page

Figure 5.11-1 continued

Part B

N-demethylated compounds originating from BYF 14182-4-hydroxy (intermediate):

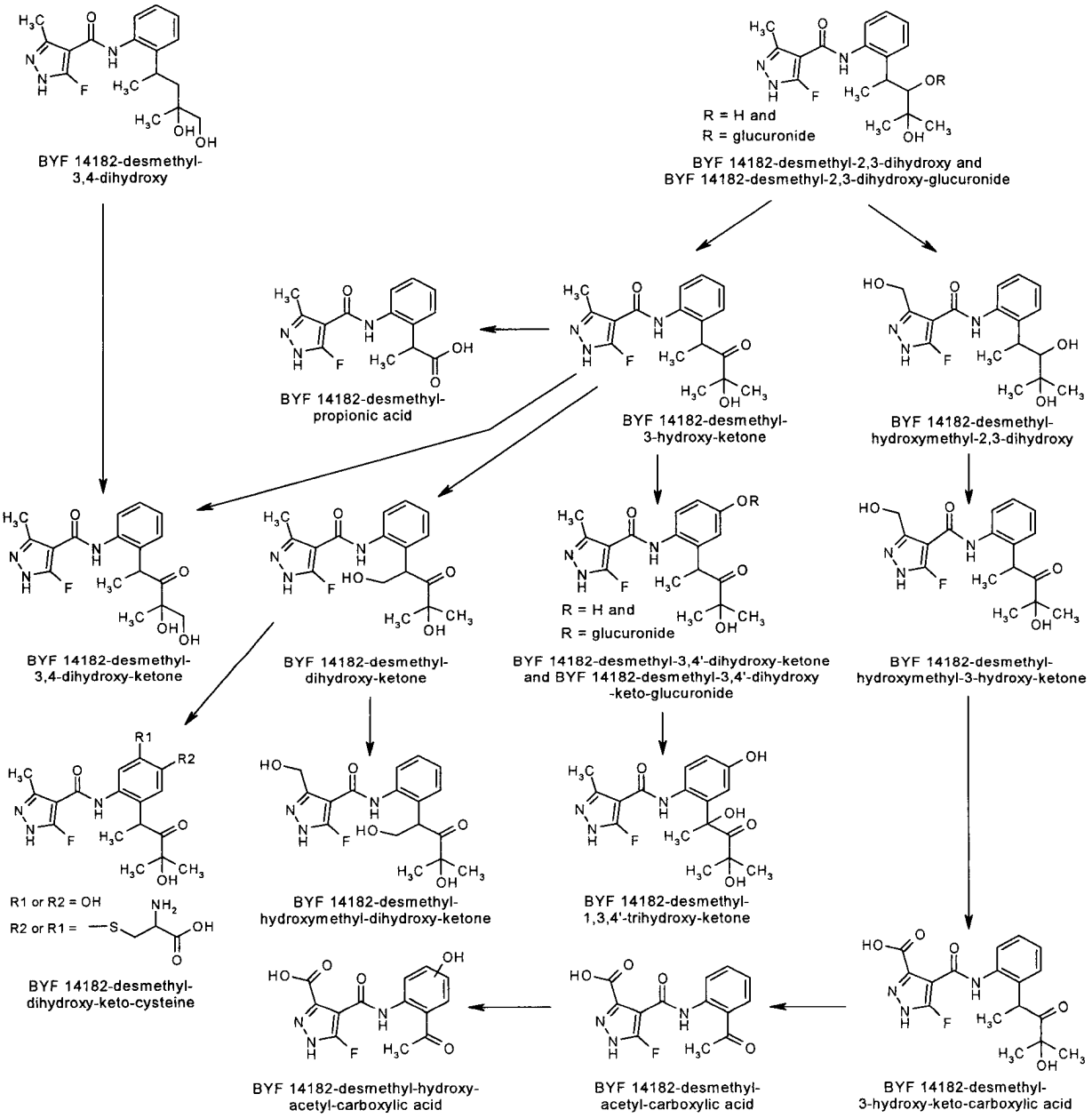


BYF 14182-desmethyl-3-hydroxy-pentanoic acid

BYF 14182-desmethyl-pentanoic acid

BYF 14182-desmethyl-hydroxymethyl-pentanoic acid

N-demethylated compounds originating from BYF 14182-3-hydroxy-butyl (intermediate):



BYF 14182-desmethyl-3,4-dihydroxy

BYF 14182-desmethyl-2,3-dihydroxy and BYF 14182-desmethyl-2,3-dihydroxy-glucuronide

BYF 14182-desmethyl-propionic acid

BYF 14182-desmethyl-3-hydroxy-ketone

BYF 14182-desmethyl-hydroxymethyl-2,3-dihydroxy

BYF 14182-desmethyl-3,4-dihydroxy-ketone

BYF 14182-desmethyl-dihydroxy-ketone

BYF 14182-desmethyl-3,4'-dihydroxy-ketone and BYF 14182-desmethyl-3,4'-dihydroxy-keto-glucuronide

BYF 14182-desmethyl-hydroxymethyl-3-hydroxy-ketone

BYF 14182-desmethyl-hydroxymethyl-dihydroxy-ketone

BYF 14182-desmethyl-1,3,4'-trihydroxy-ketone

BYF 14182-desmethyl-dihydroxy-keto-cysteine

BYF 14182-desmethyl-hydroxy-acetyl-carboxylic acid

BYF 14182-desmethyl-acetyl-carboxylic acid

BYF 14182-desmethyl-3-hydroxy-keto-carboxylic acid

2. Mutagenicity:

Thirteen Genetic Toxicology studies were performed on penflufen and/or two metabolites of the parent and were submitted by the Registrant. The tests included bacterial reverse gene mutation assays in *Salmonella typhimurium* tester strains; *in vitro* mammalian cell forward gene mutation assays in Chinese hamster lung (CHL) fibroblast V79 cells at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus, and *in vitro* chromosomal aberration test in Chinese hamster V79 cells. The parent compound (BYF 14182) was tested in initial and confirmatory assays in each of the 3 *in vitro* assays with a batch of compound used in the repeat-dose toxicity studies and with a current representative batch of the proposed specification for the BYF 14182 technical. Both metabolites BYF 14182-3-hydroxy-butyl and BYF 14182-3-pyrazolyl-AAP were also tested in each *in vitro* assay. The only *in vivo* assay (mouse bone marrow micronucleus assay) was conducted with the parent compound (BYF 14182). Neither the parent nor the two metabolites were mutagenic in bacteria or mammalian cells or clastogenic in mammalian cells. Similarly, penflufen was not clastogenic or aneugenic in whole animal bone marrow cells.

All of these studies were classified as acceptable/guideline, and they fully satisfy the requirement for mutagenicity data. At this time, there is no mutagenic concern for the parent molecule or the two metabolites. Summaries of the 13 Genetic Toxicology studies are presented below:

GENE MUTATIONS

(1) In two independent trials of the bacterial reverse gene mutation assay (MRID 48023816), BYF 14182 (95.6%) did not induce gene mutation when assayed up to concentrations that inhibited cell growth (+/-S9) in *S. typhimurium* TA1535, TA1537, TA98, TA100, or TA102 either in the plate incorporation or the pre-incubation modification of the S. *typhimurium* reverse mutation assay. Test material precipitation occurred at ≥500 µg/plate +/- S9. In the plate incorporation assay, a strain-specific bacteriotoxic effect was observed at 500 µg per plate (TA 102), 1581 µg per plate (TA 100, 102, 1535, 1537), and 5000 µg per plate (TA 100, 102, 1535, 1537). In the repeat pre-incubation assay, a strain-specific bacteriotoxic effect was observed at 5000 µg per plate (TA 100, 102, 1535).

(2) In two independent trials of the bacterial reverse gene mutation assay (MRID 48023817), BYF 14182 (94.4%) did not induce gene mutation when assayed up to the limit concentration (5000 *u*g/plate +/-S9) in *S. typhimurium* TA1535, TA1537, TA98, TA100, or TA102 either in the plate incorporation or the pre-incubation modification of the S. *typhimurium* reverse mutation assay. Test material precipitation occurred at ≥1000 µg/plate +/-S9 in both assays.

(3) In two independent trials of the bacterial reverse gene mutation assay (MRID 48023818), BYF 14182-3-hydroxy-butyl (98.5%) did not induce gene mutation when assayed up to the limit concentration (5000 *u*g/plate +/-S9) in *S. typhimurium* TA1535, TA1537, TA98, TA100, or TA102 either in the plate incorporation or the pre-incubation modification of the S. *typhimurium* reverse mutation assay. Test material precipitation occurred at 5000 µg/plate +/- S9 in both assays.

(4) In two independent trials of the bacterial reverse gene mutation assay (MRID 48023819), BYF 14182-pyrazolyl-AAP (99.6%) did not induce gene mutation when assayed up to the limit concentration (5000 *ug*/plate +/-S9) in *S. typhimurium* TA1535, TA1537, TA98, TA100, or TA102 either in the plate incorporation or the pre-incubation modification of the S. *typhimurium* reverse mutation assay. Test material precipitation occurred at ≥500 µg/plate +/- S9 in both assays.

(5) A mammalian cell forward gene mutation assay (MRID 48023820) in V79 cells at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus was conducted to evaluate the mutagenic potential of BYF 14182 (95.6% purity). The assay was performed in two independent experiments, using parallel cultures for each experimental point. Chinese hamster V79 cells were exposed to BYF 14182 at concentrations of 12.5 (Experiment 2), 25, 50, 75, 100, 125, 150, or 175 (Experiment 1) µg/mL –S9 in Experiments 1 and 2, and at concentrations of 25 (Experiment 2), 50, 75, 100, 125, 150 (Experiment 1), 175, or 200 (Experiment 1) µg/mL +S9 in Experiments 1 and 2. The treatment period in both experiments was 5 hours. Significant concentration-related cytotoxicity was observed -S9 (≥125 µg/mL) and +S9 (≥150 µg/mL), as evidenced by decreases in survival to treatment (lack of surviving cells/↓≈50%-70%) and decreases in relative population growth (lack of surviving cells/≈↓80%) following exposure. Cloning efficiency was comparable among the groups. Precipitation of BYF 14182 in the culture medium was not observed in the mutation experiments, although precipitation occurred at dose levels of 200 µg/mL, 400 µg/mL, and 800 µg/mL in the pre-test +/-S9. There was no biologically relevant increase in mutant frequency compared to that of the vehicle controls (+/- S9 mix). BYF 14182 did not induce increases in mutant frequency at concentrations up to 150 µg/mL (+S9)/100 µg/mL (-S9) in the V79/HPRT forward mutation assay.

(6) A mammalian cell forward gene mutation assay (MRID 48023821) in V79 cells at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus was conducted to evaluate the mutagenic potential of BYF 14182 (94.4% purity). The assay was performed in two independent experiments, using parallel cultures for each experimental point. Chinese hamster V79 cells were exposed to BYF 14182 at concentrations of 4.5, 9, 18, 27, or 36 µg/mL –S9 in both Experiments 1 and 2, and at concentrations of 4.7, 9.4, 18.8, 37.5, or 75 µg/mL +S9 in Experiment 1 and 18.8, 37.5, 75, 100, or 125 µg/mL +S9 in Experiment 2. The treatment period in both experiments was 4 hours. Compound precipitation was noted at ≥100 µg/mL (+S9). BYF 14182 was tested up to cytotoxic concentrations –S9 (36 µg/mL; cloning efficiency/survival <50%) and +S9 (100 µg/mL; precipitation of test material). There were no reproducible treatment-related increases in the mutant frequency with or without metabolic activation at concentrations ranging from 4.5 µg/mL to 125 µg/mL. BYF 14182 did not induce increases in mutant frequency at concentrations up to 100 µg/mL (+S9)/36 µg/mL (-S9) in the V79/HPRT forward mutation assay.

(7) A mammalian cell forward gene mutation assay (MRID 48023822) in V79 cells at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus was conducted to evaluate the mutagenic potential of BYF 14182-3-hydroxy-butyl (98.5%). The assay was performed in two independent experiments, using parallel cultures for each experimental point. Chinese hamster V79 cells were exposed to BYF 14182-3-hydroxy-butyl at concentrations of 75, 150, 300, 600, 900, or 1200 µg/mL +/-S9. The treatment period in both experiments was 5 hours. Without and with S9 mix, BYF 14182-3-hydroxy-butyl did not induce decreases in survival to treatment or in relative population growth. Precipitation of BYF 14182-3-hydroxy-butyl in the culture medium

was observed at ≥900 μg/ml –S9 and at ≥600 μg/ml +S9. There was no biologically relevant increase in mutant frequency above that of the vehicle controls either +/-S9. BYF 14182-3-hydroxy-butyl did not induce increases in mutant frequency (+/-S9), at concentration up to 1200 μg/mL (at or above the limit of solubility in the culture medium) in the V79/HPRT forward mutation assay.

(8) A mammalian cell forward gene mutation assay (MRID 48023823) in V79 cells at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus was conducted to evaluate the mutagenic potential of BYF 14182-pyrazolyl-AAP (99.6%). The assay was performed in two independent experiments, using parallel cultures for each experimental point. Chinese hamster V79 cells were exposed to BYF 14182-pyrazolyl-AAP at concentrations up to 60 μg/ml both +/-S9. The treatment period in both experiments was 5 hours. BYF 14182-pyrazolyl-AAP did not induce decreases in survival to treatment or in relative population growth either +/-S9. However, BYF 14182-pyrazolyl-AAP was tested at least up to its limit of solubility in the solvent. Precipitation of BYF 14182-pyrazolyl-AAP in the culture medium was observed at 60 μg/ml. There was no biologically relevant increase in mutant frequency (+/-S9) above that of the vehicle controls. BYF 14182- pyrazolyl-AAP did not induce increases in mutant frequency at concentrations up to 60 μg/mL (+/-S9) in the V79/HPRT forward mutation assay.

CHROMOSOME ABERRATIONS

(1) In an *in vitro* chromosome aberration test (MRID 48023824), BYF 14182 (95.6%) did not induce increases in the numbers of aberrant metaphases at concentrations up to cytotoxic levels in Chinese Hamster V79 cells exposed at concentrations of 10, 20, 40, 70, and 100 μg/mL (4 hour) and 3, 6, 12, 24, 36 μg/mL (18 hour) -S9 and at concentrations of 15, 30, 60 and 90 μg/mL (+ S9 mix; 4 hour);cultures harvested 18 hours after treatment start. Cultures were also exposed (4-hour treatment) at 40, 70, and 100 μg/mL (-S9) and 60, 75, and 90 μg/mL (+S9) and harvested 30 hours after treatment start. Without S9 mix, cytotoxic effects (reduced cell numbers/mitotic indices below 50%/precipitation) were observed at ≥10 □g/mL (4- hour treatment) and at ≥3 μg/mL (18-hour treatment). With S9 mix, cytotoxic effects (reduced cell numbers/mitotic indices below 50%/precipitation) were observed at ≥60 □g/mL. Precipitation in the medium was not observed. None of the cultures treated with BYF 14182 (+/-S9) showed biologically relevant increased numbers of aberrant metaphases. The statistically significant response at 40 μg/mL (-S9) observed following the 4-hour treatment period (18-hour harvest) was within the historical control range of the testing facility.

(2) In 2 independent *in vitro* chromosome aberration tests (MRID 48023825), BYF 14182 (94.4%) did not induce chromosomal aberrations in mammalian cells at concentrations that caused clear cytotoxicity (reduced cell numbers/mitotic indices below 50%/precipitation). Chinese hamster V79 cells were exposed at concentrations of 9.4, 18.8 and 37.5 μg/mL (4-hour treatment) and 4.7, 9.4 and 18.8 μg/mL (18-hour treatment) –S9 and at concentrations of 18.8, 37.5 and 75.0 μg/mL (+ S9 mix; 4-hour treatment). Cultures were harvested 18 hours after treatment start. In addition, cultures treated with concentrations of 100, 150 and 300 μg/mL (+S9) were harvested at 28 hours after the beginning of treatment). Without S9 mix, cytotoxic effects were observed at 37.5 μg/mL after 4 hours treatment and at ≥18.8 μg/mL after 18 hours treatment.

With S9 mix, cytotoxic effects were observed at 75 and 300 µg/ml. Precipitation in the medium was observed after treatment with 300 µg/mL +/- S9 in the first experiment. No precipitation occurred up to 300 µg/mL +/- S9 in the second experiment. None of the cultures treated with BYF 14182 (+/- S9 mix) showed biologically relevant or statistically significant increased numbers of aberrant metaphases.

(3) An *in vitro* chromosome aberration test (MRID 48023826) in Chinese hamster V79 cells was conducted to evaluate the clastogenic potential of BYF 14182-3-hydroxy-butyl (98.5%). Chinese hamster V79 cells were exposed to at concentrations of 150, 300, 600, 900, and 1200 □g/mL (4-hour treatment), and 75, 150, 300, 450, and 600 µg/mL (18-hour treatment) –S9 and at concentrations of 75, 150, 300, 600, and 900 µg/mL (4-hour treatment) +S9. Cultures of all concentrations were harvested 18 hours after treatment start. Also, cultures treated with 600, 900, and 1200 µg/mL (-S9) and 300, 600, and 900 µg/mL (+S9) were harvested 30 hours after treatment (4-hour). Concentrations were selected for metaphases reading on the basis of their cytotoxicity (reduced cell numbers/mitotic indices below 50%) and precipitation in the medium. Without S9 mix, cytotoxic effects were observed at ≥600 □g/mL after 4 hours treatment and at ≥450 µg/mL after 18 hours treatment. With S9 mix, cytotoxic effects were observed at ≥300 □g/mL. Precipitation in the medium occurred at the 4 hours treatment - S9 at ≥900 µg/ml and + S9 at 900 µg/mL. At the 18 hours treatment, precipitation in the medium occurred at 600 µg/mL. None of the cultures treated with BYF 14182-3-hydroxy-butyl +/- S9 showed biologically relevant increased numbers of aberrant metaphases. The statistically significant response at 900 µg/mL (-S9) observed following the 4-hour treatment period (18-hour harvest) was within the historical control range of the testing facility. Under the conditions of the study, BYF 14182-hydroxy-butyl did not induce increases in the numbers of aberrant metaphases at concentrations up to cytotoxic levels (≥ 900 µg/mL).

(4) An *in vitro* chromosome aberration test (MRID 48023827) in Chinese hamster V79 cells was conducted to evaluate the clastogenic potential of BYF 14182-pyrazolyl-AAP (99.6%). Chinese hamster V79 cells were exposed to BYF 14182-pyrazolyl-AAP at concentrations of 15, 30 and 60 □g/mL (4-hour and 18-hour treatments) -S9 mix and at 15, 30 and 60 µg/mL (+ S9). Cultures of all concentrations were harvested 18 hours after treatment start. In addition, cultures treated with 60 µg/mL were harvested 30 hours after treatment. Concentrations were selected for metaphases reading on the basis of their cytotoxicity (reduced cell numbers/mitotic indices below 50%) and precipitation in the medium. Without S9 mix cytotoxic effects were observed at ≥60 ug/mL after 4 hours treatment and at ≥30 ug/mL after 18 hours treatment. With S9 mix, no cytotoxic effects were observed. Precipitation in the medium occurred –S9 at 30 ug/mL and above (4 hours treatment) and at 60 ug/mL (18 hours treatment). Precipitation in the medium occurred at 60 ug/mL +S9. None of the cultures treated with BYF 14182-pyrazolyl-AAP +/-S9 showed biologically relevant or statistically significant increased numbers of aberrant metaphases. There were no biologically relevant increases in the numbers of metaphases with aberrations for any treatment condition. The statistically significant response observed at 30 µg/mL (18-hour treatment; 18-hour harvest) was within the historical control range for DMSO. BYF 14182-pyrazolyl-AAP did not induce increases in the numbers of aberrant metaphases at concentrations up to cytotoxic levels (60 µg/mL) in mammalian cells *in vitro*. BYF 14182-pyrazolyl-AAP is considered not to be clastogenic for mammalian cells in vitro.

MICRONUCLEUS ASSAY

In a bone marrow micronucleus assay (MRID 48023828), four groups of 5 male Crl:NMRI BR mice were administered BYF 14182 (Batch no. 2005-004498; 95.6% purity) suspended in 0.5% aqueous Cremophor emulsion twice *via* the intraperitoneal (i.p.) route at doses of 0 (0.5% aqueous Cremophor emulsion), 250, 500 and 1000 mg/kg bw, separated by 24 hours. Positive control mice received a single i.p. injection of cyclophosphamide (20 mg/kg bw). Bone marrow from one femur from each rat was sampled 24 hours after the last injection. Two thousand polychromatic erythrocytes (PCEs) were examined per rat, and the number of normochromatic erythrocytes (NCEs) per 2000 PCEs was determined. Slides of bone marrow cells were prepared and scored for the occurrence of micronucleated polychromatic erythrocytes (MPCEs), micronucleated normochromatic erythrocytes, and PCE/total erythrocytes ratios. All mice survived until the end of the study but showed symptoms of toxicity (apathy, roughened fur, body weight loss, sternal recumbency, spasm, difficulty in breathing, and slitted eyes) at all dose levels. There was an increase in NCE to PCEs at all test doses and the increase was significant at the mid-dose; however, the relevance, if any, of this finding is not clear because the response was not dose-related. There were no biologically significant variations in the incidence of MPCEs between the control and the BYF 14182 treated mice. Under the conditions of the study, there was no indication of a clastogenic or aneugenic effect of BYF 14182 in the male mouse micronucleus test at dose levels up to those producing clear evidence of overt toxicity.

3. Structure Activity Relationship

No structural alerts were identified in DEREK.

4. Subchronic and Chronic Toxicity

a) Subchronic

(1) In a subchronic oral toxicity study (MRID 48023805), BYF 14182 (batch number NLL 7306-18, 98.6% purity) was administered continuously *via* dietary administration to groups of Wistar rats (10/sex/group) at concentrations of 0, 150, 7000, or 14000 ppm (equivalent to 0, 9.5, 457 and 949 mg/kg/day in males and 0, 11.4, 492 and 1009 mg/kg/day in females) for at least 90 days. This study is a companion study to MRID 48023806 (SA 05148, M-273186-01-2), which is a 90-day dietary study that was performed using dose levels of 0, 50, 150, or 3500 ppm (equivalent to 0, 3.2, 9.3 or 228 mg/kg/day in males and 0, 3.7, 11.4 or 260 mg/kg/day in females).

No treatment-related mortalities or clinical signs of toxicity (including the neurotoxicological assessment) were observed during the study in either sex. Body weight was comparable among the male groups throughout the study, although body weight gain was significantly reduced by 24% in males at 14000 ppm during the first week of treatment. Thereafter, body weight changes were similar to controls. In females, body weight was slightly reduced over the entire treatment period (5% to 7%) at 7000 ppm and 14000 ppm. During the first week of treatment, body weight gain was reduced in females by 36% at 7000 ppm and 55% at 14000 ppm. With continued exposure, the weekly body weight gain was comparable among the groups through 7 weeks. On Day 90, the overall mean reduction in body weight gain was 17%

at 7000 ppm and 12% at 14000 ppm, when compared to controls, but there was no dose response. Mean food consumption was reduced over the entire treatment period at 7000 ppm (8% to 17%) and 14000 ppm (5% to 14%) compared to controls.

Higher total cholesterol concentration, globulin concentration, and gamma-glutamyltransferase activity and lower albumin/globulin ratio were observed in both sexes at 7000 ppm and 14000 ppm. Higher total protein concentration (7000 ppm and 14000 ppm) and albumin concentration (14000 ppm) were observed in males. Lower mean alanine aminotransferase and/or aspartate aminotransferase activities were observed in both sexes at 14000 ppm. In females at 7000 ppm and 14000 ppm, lower total bilirubin concentrations were observed.

At necropsy, mean absolute and relative liver weights were increased in males and females at 14000 ppm and to a lesser extent at 7000 ppm. Enlarged livers were observed in all rats at 14000 ppm and in 8/10 males and 7/10 females at 7000 ppm.

Centrilobular hepatocellular hypertrophy was observed in all rats of both sexes at 7000 ppm and in 9/10 males and all females at 14000 ppm, compared to none in either sex in the control and 150 ppm groups. In the thyroid, 8/10 males at both the 7000 ppm and 14000 ppm dose levels, and 6/10 females at 14000 ppm had thyroid follicular cell hypertrophy, and 3/10 males at both the 7000 ppm and 14000 ppm dose levels had altered colloid. In the kidney, an increased incidence of hyaline droplet accumulation was noted in 6/10 males at 14000 ppm and in 5/10 males at 7000 ppm.

In this definitive 90-day rat study (MRID 48023805), together with the findings of MRID 48023806 (point KIIA 5.3.2/02), it was concluded that the Lowest Observed Adverse Effect Level (LOAEL) was not identified. The findings at 14000 ppm (equivalent to 949 mg/kg/day in males and 1009 mg/kg/day in females) included an increase in total cholesterol concentration and gamma-glutamyltransferase activity in both sexes, an increase in the incidence of centrilobular hepatocellular hypertrophy, which was correlated with higher liver weights and macroscopically enlarged livers in both sexes, an increased incidence of thyroid follicular cell hypertrophy in both sexes, and altered colloid in males. These effects are considered an adaptive response and not adverse.

This study is classified as totally reliable (acceptable/guideline), and it satisfies the guideline requirement for a subchronic oral toxicity study (OPPTS 870.3100; OECD 408) in rats.

(2) In a subchronic oral toxicity study (MRID 48023806), BYF 14182 (batch number NLL 7306-18, 98.2 to 98.8% purity) was administered *via* the diet to groups of Wistar rats (10/sex/group) at dietary concentrations of 0, 50, 150, and 3500 ppm (equivalent to 0, 3.2, 9.3 and 228 mg/kg/day in males and 0, 3.7, 11.4 and 260 mg/kg/day in females) for at least 90 days. In this study, only the kidney, liver, pancreas, pituitary and thyroid glands were examined at microscopy, and no hematology, urinalysis, ophthalmological, or neurotoxicological examinations were performed. This study was performed to provide additional information on the potential toxic effects of BYF 14182 observed in a similar subchronic oral toxicity study in rats (MRID 48023805). Both studies were performed to provide information for selection of dose levels for future toxicity studies in the rat.

No treatment-related mortalities or clinical signs of toxicity were observed during the study.

No treatment-related body weight or food consumption changes were observed at any dose level throughout the study. Clinical chemistry parameters were not affected.

At necropsy, mean terminal body weight in females at 3500 ppm was decreased by 6% when compared to control rats. Mean absolute and relative liver weights were increased by 13% to 15% in males and 8% to 16% in females. Enlarged livers were observed in 4/10 females at 3500 ppm.

Increased liver weights were observed in both sexes at 3500 ppm, which is consistent with the minimal centrilobular hepatocellular hypertrophy observed in both sexes at 3500 ppm. This finding was considered to be an adaptative response and not an adverse effect, based on a lack of accompanying alterations in relevant clinical chemistry parameters and adverse lesions. There was an increase in thyroid weight in both sexes, mainly at the 3500 ppm dose level, but these changes were not accompanied by any microscopic findings. In the kidney, minimal tubular hyaline droplets were observed in males at 3500 ppm.

A Lowest Observed Adverse Effect Level (LOAEL) was not identified in this study. At the highest dose tested (3500 ppm, equivalent to 228 mg/kg/day in males and 260 mg/kg/day in females), increased liver weights and an increased incidence of centrilobular hepatocellular hypertrophy were observed, which were not accompanied by alterations in relevant clinical chemistry parameters or adverse liver lesions. The effects observed are considered adaptive and not adverse over this time frame.

This subchronic oral toxicity study is classified acceptable/non-guideline and alone does not satisfy the guideline requirement for a subchronic oral toxicity study in the rat. It is non-guideline because only the kidney, liver, pancreas, pituitary and thyroid glands were examined microscopically, and hematology, urinalysis, or ophthalmological examinations were not performed. When considered together with MRID 48023805 (Report No. SA04199), this guideline requirement (OPPTS 870.3100; OECD 408) is satisfied.

(3) In an oral toxicity study (MRID 48023838), BYF 14182 (batch numbers NLL7306-15 and NLL7306-3.1: 99.2 and 99.4% purity, respectively) was administered continuously *via* the diet to groups of Wistar rats (5/sex/group) for at least 28 days at concentrations of 0 (untreated diet), 150, 2000 and 7000 ppm (equivalent to 12, 154 and 560 mg/kg/day in males and 13, 169 and 648 mg/kg/day in females).

There were no mortalities or clinical signs of toxicity observed during the study. Body weights and body weight gains were comparable among the male groups. In high dose females, mean body weight was slightly reduced (3% to 7%) throughout the study. The overall mean cumulative body weight gain on Day 28 was reduced by 12%, when compared to controls. Mean food consumption was slightly reduced in females throughout treatment, with an overall reduction of 9%. Mean body weights in females at 2000 ppm were comparable to controls. The overall mean cumulative body weight change on Day 28 was reduced by 16%. Mean food consumption was comparable to controls in females between Days 1-8, but was slightly reduced thereafter, with an overall reduction of 9%.

There was a dose-related increase in total cholesterol concentration in females (↑27% at 2000 ppm; ↑31% at 7000 ppm) compared to controls.

The liver was a target organ with higher liver weights in both sexes associated with centrilobular hepatocellular hypertrophy in most of the rats. These effects were mainly seen at 7000 ppm and to a lesser extent at 2000 ppm. In addition, slightly higher kidney microscopic findings characteristic of hyaline droplet nephropathy were observed in high dose males, although this finding is known to be rat-specific and not relevant for humans.

Regarding hepatotoxicity parameters, BYF 14182 was found to be a cytochrome P-450 inducer with a phenobarbital-like profile, the hepatic total cytochrome P-450 content, BROD and PROD related activities being increased in both sexes at 7000 ppm and to a lesser extent at 2000 ppm.

A Lowest Observed Adverse Effect Level (LOAEL) was not identified in this 28-day exposure study. The liver was identified as a major target organ for BYF 14182 (dose-related increase total P-450, BROD, and PROD activities in both sexes, increased cholesterol levels in females, increased liver weight in both sexes, increased incidence of hepatocellular hypertrophy in both sexes). The liver effects are considered adaptive and not adverse.

This 28-day oral toxicity study is classified as acceptable/non-guideline. The study was performed to provide information for dose selection for longer-term studies in mice. It does not satisfy any guideline requirement.

(4) In an oral toxicity study (MRID 48023839), BYF 14182 (batch number NLL 7306-18: 98.6% purity) was administered *via* the diet to groups of C57BL/6J mice (5/sex/group) at dose levels of 0, 150, 3500 and 7000 ppm (equivalent to 0, 26, 632 and 1274 mg/kg body weight/day in males and 0, 31, 741 and 1585 mg/kg body weight/day in females, respectively) for at least 28 days.

There were no mortalities or treatment-related clinical signs of toxicity in either sex. Body weight and body weight gains were comparable among the male groups. In females, body weight was comparable among the female groups, although a lower body weight gain during weeks 1 (↓37%) and 2 (↓60%) resulted in a slight decrease in body weight at day 15 (↓7%). Thereafter, body weight change was equal to or greater than in the control group.

There was an increase in the incidence of centrilobular hepatocellular hypertrophy at 7000 ppm, which was correlated with increased liver weights and macroscopically enlarged livers in both sexes. A dose-related increase in alkaline phosphatase activity was observed in both sexes, although statistical significance was attained only in the 7000 ppm females. A statistically significant decrease in total cholesterol was observed in both sexes, although there was no dose response in females. Alanine aminotransferase activity was increased at all dose levesls in both sexes, but neither sex displayed a dose-response. Females displayed a dose-related (slight) decrease in total protein concentration. The effects observed are considered an adaptive response, and the highest dose is greater than the limit dose for both sexes.

A Lowest Observed Adverse Effect Level (LOAEL) was not identified in this study, which included a dose level that exceeded the limit dose in both sexes. The liver effects and associated clinical chemistry findings at 7000 ppm (equivalent to 1274 mg/kg/day in males and 1585 mg/kg/day in females) are considered adaptive and not adverse.

This study is classified as acceptable/non-guideline. The study was performed to provide information for dose selection for longer-term studies in mice. It does not satisfy any guideline requirement.

(5) In a subchronic oral toxicity study (MRID 48023807), BYF 14182 (batch number NLL 7306-18, 98.8% purity) was administered continuously *via* dietary administration to groups of C57BL/6J mice (10/sex/group) at concentrations of 0, 150, 3500 and 7000 ppm (equivalent to 0, 26.9, 638 and 1238 mg/kg/day in males and 0, 31.5, 757 and 1600 mg/kg/day in females) for at least 90 days.

No mortalities or treatment-related clinical signs of toxicity were observed during the study. Body weight and food consumption parameters were comparable among the groups for both sexes throughout the study.

There was a dose-related decrease in total cholesterol concentration in males and females at the 3500 ppm and 7000 ppm dose levels. Alanine aminotransferase was increased in both sexes at 7000 ppm (males ↑35%/females ↑48%), although statistical significance was not attained in the males.

At necropsy, there was a dose-related increase in mean absolute and relative liver weights in both sexes at 3500 ppm and 7000 ppm. Enlarged livers were observed in 9/10 males and 8/10 females at 7000 ppm and 5/10 males and 1/10 females at 3500 ppm. Consistent with these findings was the increased incidence of minimal to mild diffuse centrilobular hepatocellular hypertrophy observed in 9/10 males and 7/10 females at 7000 ppm and 4/10 males and 4/10 females at 3500 ppm.

A Lowest Observed Adverse Effect Level (LOAEL) was not identified in this study, which included a dose level that exceeded the limit dose in both sexes (7000 ppm; equivalent to 1238 mg/kg/day in males and 1600 mg/kg/day in females). The liver effects are considered adaptive and not adverse.

This subchronic oral toxicity study is classified acceptable/guideline, and it satisfies the guideline requirement (OPPTS 870.3100; OECD 408) for a subchronic oral toxicity study in the rodent.

b. Chronic

(1) In a chronic toxicity/carcinogenicity study (MRID 48023815), BYF 14182, (Batch No. 2005-004498, 95.6% purity) was administered *via* the diet to groups of Wistar rats at 0, 100, 2000 and 7000 ppm, corresponding to 0, 4.0, 79 and 288 mg/kg/day in males and 0, 5.6, 113 and 399 mg/kg/day in females over a 24-month treatment period (10 rats/sex/group designated for the interim sacrifice after 52 weeks, 10 rats/sex/group designated for the recovery group sacrificed after 65 weeks following 52 week of treated diet, and 13 weeks of untreated diet, and 60 rats/sex/group designated for the final sacrifice after 104 weeks).

No treatment-related mortality or clinical signs of toxicity were observed in either sex at any dose level. Body weights and body weight gains were comparable among the male groups throughout the study. Treatment-related decreases in body weights and body weight gains were observed in females at 2000 ppm and 7000 ppm, and the body weight deficits increased with time of exposure. During the first week of exposure, a dose-related reduction in body weight gain was observed in females at 2000 ppm (↓25%) and 7000 ppm (↓58%), whereas the reduction over the first 90 days was ↓10% and ↓20%, respectively. At study termination, a 12% decrease in body weight was observed in females at 7000 ppm, and overall body weight gain was decreased by 18% compared to the control. Food consumption was consistent with the lower body weight observed. No differences on body weight, body weight gain, or food consumption were observed at the end of the recovery period.

There was a dose-related increase in mean total cholesterol concentrations in females during the first year of treatment only, whereas treated males displayed lower cholesterol values compared to the controls but there was no dose-response. Decreases in alkaline phosphatase activity, aspartate aminotransferase activity, and alanine aminotransferase activity were observed in both sexes at 7000 ppm throughout the study.

At the end of the chronic phase (12 months), there was a dose-related increase in liver weight in both sexes when compared to controls. In females at 2000 ppm and both sexes at 7000 ppm, there was an increased incidence of enlarged livers. At 7000 ppm, a higher incidence of centrilobular to panlobular hepatocellular hypertrophy and centrilobular hepatocellular macrovacuolation was observed in both sexes, and a higher incidence of hepatocellular brown pigments was observed in females only. In the thyroid gland, a higher incidence of enlarged thyroid glands was observed at 7000 ppm, which correlated with a higher incidence of follicular cell hypertrophy observed in both sexes and a higher incidence of colloid alteration was observed in females. The liver and the thyroid gland microscopic findings were mostly reversible as liver hypertrophy was not observed after the 3-month recovery period and only one male rat presented a minimal follicular cell hypertrophy at the end of the recovery period.

At the end of the carcinogenicity phase (24 months), females at 7000 ppm showed increased thymus weights, although statistical significance was not attained. Both sexes at 7000 ppm displayed increased liver weights (absolute and/or relative) compared to controls. Treatment-

related macroscopic findings consisted of enlarged livers and dark livers in the both sexes, white focus in the liver in females only, and dark thyroid glands in both sexes.

There was a dose-related increase in the incidence of centrilobular to panlobular hepatocellular hypertrophy and of centrilobular hepatocellular macrovacuolation in both sexes, and females displayed a higher incidence of hepatocellular brown pigments. In the thyroid gland, a higher incidence of follicular cell hypertrophy and colloid alteration was observed in both sexes. A higher incidence of follicular brown pigments was observed in females at 7000 ppm.

The findings at 7000 ppm (equivalent to 288 mg/kg/day weight/day in males and 399 mg/kg body weight/day in females) included decreased body weight/body weight gain in females, increased liver weight in both sexes, increased incidence of centrilobular to panlobular hepatocellular hypertrophy and of centrilobular hepatocellular macrovacuolation in both sexes, increased incidence of hepatocellular brown pigment in females, colloid alteration in the thyroid in females, and increased cholesterol in females. These effects are considered an adaptive response and not adverse. However, the dosing is considered adequate due to the presence of treatment-related tumors.

This chronic toxicity/carcinogenicity study is classified as acceptable/guideline, and it satisfies the guideline requirement (OPPTS 870.6200; OECD 424) for a chronic toxicity/carcinogenicity study in the rat. Available data suggest that the limit dose (20000 ppm) would have been tolerated.

(2) In a carcinogenicity study (MRID 48023814), BYF 14182 (Batch No. 2005-004498, 95.6% purity) was administered *via* the diet to C57BL/6J mice (60/sex/group) at dose levels of 0, 100, 1000 or 6000 ppm (equivalent to 0, 14.3, 146, and 880 mg/kg/day in males and 0, 18.4, 182, and 1101 mg/kg/day in females) for 52 weeks. After 52 weeks (chronic phase), 10 mice/sex/group were sacrificed (interim sacrifice). The remaining 50 mice/sex/group continued treatment until the scheduled final sacrifice following at least 78 weeks of treatment (carcinogenicity phase).

There were no treatment-related effects on mortality or clinical signs of toxicity in either sex. Slight decreases (↓6%-7%%) in overall body weight gains were observed in both sexes at 6000 ppm, but terminal body weights were comparable to the control for both sexes. Initial body weight gain was significantly decreased (↓27%) in females at 6000 ppm, and males at 6000 ppm displayed a reduced body weight gain (↓18%) over the first 6 weeks.

There was a dose-related decrease in mean total leucocyte (↓30% and ↓36%) and absolute lymphocyte (↓26% and ↓37%) counts in males at 1000 ppm and 6000 ppm, respectively, at 13 months. Females at 6000 ppm also showed decreases in mean total leucocyte (↓24%) and absolute lymphocyte (↓23%) counts at 13 months, but statistical significance was not attained.

At the 12-month sacrifice, increased liver weights were observed in both sexes at 6000 ppm compared to the controls. Enlarged liver was observed in 2/10 males and 6/9 females. Pale liver was observed in 1/10 males and 3/9 females. Histopathological examinations were not performed at this time point.

At the 18-month terminal sacrifice, increased absolute and relative liver weights were observed in both sexes at 6000 ppm. Enlarged livers were observed in 2/45 males and 33/45 females. In addition, enlarged thyroid glands were found in 9/45 females. These findings were correlated with treatment-related microscopic changes in the liver and the thyroid gland. There was a dose-related increase in the incidence and/or severity of diffuse centrilobular hepatocellular hypertrophy in both sexes. An increased incidence of hepatocellular vacuolation was observed in males at 6000 ppm, whereas a higher severity of hepatocellular vacuolation was observed in all female groups compared to the control. Additionally, females showed a higher incidence and severity of diffuse, mainly periportal, hepatocellular macrovacuolation at 6000 ppm. In the thyroid, a higher incidence and severity of follicular cell hyperplasia was observed in 38/50 females at 6000 ppm compared to 23/50 females in the control group.

Treatment-related increased liver weights associated with histopathological findings were observed in the liver in both sexes at all dose levels. These liver effects were associated with thyroid effects and are considered an adaptive response and not adverse.

A Lowest Observed Adverse Effect Level (LOAEL) was not identified in this study, which included a dose level that exceeded the limit dose in females and one that was close to the limit dose in males. The liver effects and associated effects on the thyroid are considered adaptive and not adverse. In the subchronic oral toxicity study in mice at a somewhat higher dose level (7000 ppm; 1238 mg/kg/day and 1600 mg/kg/day), a similar liver response was observed, indicating that continued exposure does not result in additional/more severe toxicity. Exposure of mice to BYF 14182 at dose levels greater than or near the limit dose for a period of 78 weeks did not result in an increase in the incidence of any tumor type in either sex.

This carcinogenicity study is classified acceptable/guideline, and it satisfies the guideline requirement (870.4200; OECD 451) for a carcinogenicity study in the mouse.

5. Mode of Action

A formal mode of action framework for the tumors identified was not provided by the registrant for consideration by the CARC.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

The Committee considered the following for a weight-of-evidence determination of the carcinogenic potential of penflufen.

1. Carcinogenicity

Rat

• *Hemolyphoreticular Tumors:* Male Wistar rats had a statistically significant trend, and a significant pair-wise comparison of the 7000 ppm dose group with the controls, for histiocytic sarcomas, both at $p < 0.05$. The historical control incidence of histiocytic sarcoma from the testing lab in male Wistar Rj:WI(IOPS HAN) rats ranged from 0 to 3.3%, with a mean of 0.8%. The concurrent control value was within the historical control range, while the tumors seen at the high dose (9%) exceeded the historical control range (0-3.3%). The CARC considered the histiocytic sarcomas to be treatment-related in male rats.

• *Brain Astrocytomas:* While there were no statistically significant differences in the incidence of brain astrocytomas in male rats, these were fatal tumors. The astrocytomas in the 7000 ppm male rats appeared in unscheduled sacrifice rats dying on test days 429, 520, and 687, with no concomitant increase in terminal sacrifice rats. The astrocytomas in the control and 100 ppm males were found at the scheduled sacrifice (day 733). The incidences in the control and 100 ppm groups (both 2%) were within the historical control range (0- 3.7%), but the incidence at 7000 ppm (5%) was outside the historical control range of 0-3.8%. The CARC considered the brain astrocytomas to be treatment-related in male rats despite the lack of statistical significance and the small tumor increase, since brain astrocytomas are considered to be rare and were fatal tumors.

• *Ovarian tubulostromal Tumors:* Female rats had statistically significant trends in ovarian tubulostromal adenomas at $p<0.01$ and in ovarian tubulostromal combined adenomas and/or adenocarcinomas at $p<0.05$. There were no statistically significant pair-wise comparisons of the dosed groups with the controls. The incidence of adenomas at the high dose exceeded the historical control range (0-6.7%) of the laboratory. The CARC considered the ovarian tumors to be treatment-related in female rats.

• *Adequacy of Dosing:* Dosing at the 7000 ppm (288/399 mg/kg/day, M/F) is considered adequate in both male and female rats due to the presence of treatment-related tumors.

Mouse

• There were no treatment-related increases in tumors in either male or female mice.

• *Adequacy of Dosing:* Dosing at the high dose of 6000 ppm (880/1101 mg/kg/day, M/F) was considered to be adequate in both sexes of mice since it was close to the limit dose in males and exceeded the limit dose in females. The effects seen at the high dose were considered to be adaptive and not adverse, and there was no evidence of tumors.

2. Mutagenicity: There is no concern for mutagenicity.

3. Structure Activity Relationship: No structural alerts were identified.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified penflufen as "Suggestive Evidence of Carcinogenic Potential." This classification was based on the presence of a statistically significant increase in histiocytic sarcomas (significant trend and pair-wise comparison of high dose group with controls) in male rats, but in the absence of a dose response and a lack of pre-neoplastic lesions. In addition, a marginal increase in brain astrocytomas, a fatal tumor, was also observed in male rats at the high dose, however, this effect was not dose-related and did not reach statistical significance (i.e., there was no trend or pair-wise significance). In addition, there were no pre-neoplastic lesion such as glial proliferation which is a good indicator of chemical tumor induction (i.e, there will be changes in the cells prior to transformation to a neoplasm). The ovarian adenomas observed at the high dose also showed no dose response, no pair-wise significance, no decrease in latency, and there were no pre-neoplastic lesions such as hyperplasia of the epithelial cells of the endometrium. Additionally, there was no evidence of carcinogenicity in male or female mice (at doses that were judged to be adequate to assess the carcinogenic potential), no concern for mutagenicity (*in vivo* or *in vitro*) for the parent molecule or the two metabolites, and there were no other lines of evidence (such as structure-activity relationship). Although these three tumors were considered treatment-related and raised a concern, they provided weak evidence of carcinogenicity (i.e. marginal tumor responses), and, therefore, a stronger conclusion for carcinogenic potential could not be supported. Thus, the weight of evidence is suggestive of carcinogenic potential for penflufen.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

The evidence from animal data is suggestive of carcinogenicity which raises a concern for carcinogenic effects but is judged not sufficient for quantification of cancer risk in humans. Also, according the *Guidelines,* when there is a "Suggestive" classification, the Agency does not attempt a dose-response assessment as the nature of the data generally would not support one. Therefore, the Agency has determined that quantification of risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to penflufen.

VIII. Bibliography

Table. 4.	Bibliography of Submitted Toxicity Studies for Penflufen (BYF 14182)
MRID	**Citation**
	Toxicology Studies
48023805	Steiblen, G. (2006) BYF 14182 - 90-Day Toxicity Study in the Rat by Dietary Administration. Project Number: M/273186/01/2, SA/04199, M/273186/01/2/OCR. Unpublished
48023806	Steiblen, G. (2006) BYF 14182 - 90-Day Toxicity Study in the Rat by Dietary Administration - Complementary Study. Project Number: M/273644/01/2, SA05148, M/273644/01/2/OCR. Unpublished
48023807	Steiblen, G. (2006) BYF 14182 - 90-Day Toxicity Study in the Mouse by Dietary Administration. Project Number: M/309584/01/2, SA/05029, M/309584/01/2/OCR. Unpublished
48023808	Kennel, P. (2008) BYF 14182: 90-Day Toxicity Study in the Dog by Dietary Administration. Project Number: M/298785/01/2, SA/06327, M/298785/01/2/0CR. Unpublished
48023809	Sheets, L. (2009) A Subacute Dermal Toxicity Study in Rats with BYF 14182. Project Number: M/352352/01/1, 202021, 08/S22/OQ. Unpublished
48023810	Langrand-Lerche, C. (2008) BYF 14182 - Developmental Toxicity Study in the Rat by Gavage. Project Number: M/307168/01/3, SA/06329, LYNX/PSI/N/TXELP017. Unpublished
48023811	Kennel, P. (2008) BYF 14182 - Developmental Toxicity Study in the Rabbit by Gavage. Project Number: M/307955/01/2, SA/06330, LYNX/PSI/N/TXELP019. Unpublished
48023812	Milius, A. (2009) Technical Grade BYF 14182: A Two-Generation Reproductive Toxicity Study in the Wistar Rat: Final Report. Project Number: M/357261/01/1, 07/R72/MK, M/357261/01/1/OCR. Unpublished
48023813	Kennel, P. (2009) BYF 14182 - Chronic Toxicity Study in the Dog by Dietary Administration. Project Number: M/349926/01/2, SA/06328, LYNX/PSI/N/TXELP022. Unpublished
48023814	Odin-Feurtet, M. (2009) Carcinogenicity Study of BYF 14182 in the C57BL/6J Mouse by Dietary Administration. Project Number: M/357859/01/2, SA/06326, LYNX/PSI/N/TXELP024. Unpublished
48023815	Rascle, J. (2009) Chronic Toxicity and Carcinogenicity Study of BYF 14182 in the Wistar Rat by Dietary Administration. Project Number: M/357848/01/2, SA/06115, LYNX/PSI/N/TXELP003. Unpublished
48023816	Herbold, B. (2007) BYF 14182: Salmonella/Microsome Test - Plate Incorporation and Preincubation Method. Project Number: M/295834/01/2, AT04290, T/8077202. Unpublished.
48023817	Sokolowski, A. (2009) Salmonella typhimurium Reverse Mutation Assay with BYF 14182. Project Number: M/355090/01/2, 1271801, M/355000/01/2/OCR. Unpublished
48023818	Herbold, B. (2008) BYF 14182-3-Hydroxy-Butyl (Project: BYF 14182) - Salmonella/Microsome Test - Plate Incorporation and Preincubation Method. Project Number: M/306566/01/2, AT04777, TXELP042. Unpublished
48023819	Herbold, B. (2009) BYF 14182-Pyrazolyl-AAP - (Project: BYF 14182) -

Table. 4.	Bibliography of Submitted Toxicity Studies for Penflufen (BYF 14182)
MRID	**Citation**
	Salmonella/Microsome Test Plate Incorporation and Preincubation Method. Project Number: M/349984/01/2, AT05286, T/1080085. Unpublished
48023820	Entian, G. (2007) BYF 14182: V79/HPRT Test in vitro for the Detection of Induced Forward Mutations. Project Number: M/295851/01/2, AT04328, M/295851/01/2/OCR. Unpublished
48023821	Wollny, H. (2009) Gene Mutation Assay in Chinese Hamster V79 cells in vitro (V79 / HPRT) with BYF 14182. Project Number: M/358056/01/2, 1271802, M/358056/01/2/OCR. Unpublished.
48023822	Entian, G. (2008) BYF 14182-3-Hydroxy-Butyl (Project: BYF 14182) - V79/HPRT-Test in vitro for the Detection of Induced Forward Mutations. Project Number: M/302723/01/2, AT04610, T/4078702. Unpublished.
48023823	Entian, G. (2009) BYF 14182-3-Pyrazolyl-AAP: V79/HPRT-Test in vitro for the Detection of Induced Forward Mutations. Project Number: M/355623/01/2, AT05453, TXELP111. Unpublished
48023824	D'Acquisto, M. (2007) BYF 14182: in vitro Chromosome Aberration Test with Chinese Hamster V79 Cells. Project Number: M/294392/01/2, AT04201, T/9077203. Unpublished
48023825	Hall, C. (2009) In vitro Chromosome Aberration Test in Chinese Hamster V79 Cells with BYF 14182. Project Number: M/355092/01/2, 1271803, M/355092/01/2/OCR. Unpublished
48023826	Nern, M. (2008) BYF 14182-3-Hydroxy-Butyl: in vitro Chromosome Aberration Test with Chinese Hamster V79 Cells. Project Number: M/304932/01/2, AT04638, M/304932/01/2/OCR. Unpublished
48023827	Thum, M. (2009) BYF 14182-Pyrazolyl-AAP: in vitro Chromosome Aberration Test with Chinese Hamster V79 Cells. Project Number: M/356328/01/2, AT05509, T/2080086. Unpublished
48023828	Herbold, B. (2007) BYF 14182: Micronucleus-Test on the Male Mouse. Project Number: M/299229/01/2, AT04397, T/2077981. Unpublished
48023829	Hoss, H. (2009) An Acute Oral Neurotoxicity Screening Study with Technical Grade BYF 14182 in Wistar Rats. Project Number: M/328497/01/1, 201967, 07/N12/MH. Unpublished.
48023830	Gilmore, R. (2009) A Subchronic Neurotoxicity Screening Study with Technical Grade BYF 14182 in Wistar Rats. Project Number: M/328503/01/1, 201961, 07/N72/LA. Unpublished
48023831	Bongartz, R.; Miebach, D. (2009) [Phenyl-UL-(Carbon 13)/(Carbon 14)]BYF 14182: Absorption, Distribution, Excretion and Metabolism in the Rat. Project Number: M/352042/01/2, MEF/08/175, M1824534/7. Unpublished
48023832	Bongartz, R.; Miebach, D. (2009) [Pyrazole-3-(Carbon 14)]BYF 14182: Absorption, Distribution, Excretion and Metabolism in the Rat. Project Number: M/348815/01/2, MEF/08/176, M1824533/6. Unpublished
48023833	Koester, J. (2009) Quantitative Whole Body Autoradiography of [Phenyl-UL-(Carbon 13)/(Carbon 14)]BYF 14182 in Male and Female Rats: Distribution of Radioactivity and Elimination from Blood, Organs and Tissues After Single Oral Administration Including Determination of Radioactivity in the Excreta and Exhaled ((Carbon 14) Carbon Dioxide). Project Number: M/345178/01/2, MEF/08/162, M1811491/5. Unpublished

Table. 4.	Bibliography of Submitted Toxicity Studies for Penflufen (BYF 14182)
MRID	**Citation**
48023834	Koester, J. (2009) Quantitative Whole Body Autoradiography of [Pyrazole-3-(Carbon 14)]BYF 14182 in Male and Female Rats: Distribution of Radioactivity and Elimination from Blood, Organs and Tissues After Single Oral Administration Including Determination of Radioactivity in the Excreta and Exhaled ((Carbon 14) Carbon Dioxide). Project Number: M/344803/01/2, MEF/08/179, M1811667/0. Unpublished
48023835	Koester, J. (2009) [Phenyl-UL-(Carbon 13)/(Carbon 14)]BYF 14182 - Metabolism in Organs and Tissues of Male and Female Rats (3 Time-Points). Project Number: M/354487/01/2, MEF/09/475, M1824542/6. Unpublished
48023836	Bongartz, R.; Miebach, D. (2009) [Pyrazole-3-(Carbon 14)]BCS-AA10006 (BYF 14182-3-Hydroxy-Butyl) - Absorption, Distribution, Excretion and Metabolism in the Rat. Project Number: M/354679/01/2, MEF/09/376, M1824556/1. Unpublished
48023837	Schladt, L.; Vohr, H. (2008) BYF 14182 - Subacute Oral Immunotoxicity Study in Wistar Rats (4 Weeks Administration by Diet). Project Number: M/307722/01/2, AT04807, TXELP029. Unpublished
48023838	Steiblen, G. (2004) BYF 14182: Exploratory 28-Day Toxicity Study in the Rat by Dietary Administration: Final Report. Project Number: M/080714/01/2, SA/03339, M/080714/01/2/OCR. Unpublished
48023839	Rascle, J. (2005) BYF 14182 - Preliminary 28-Day Toxicity Study in the Mouse by Dietary Administration: Final Report. Project Number: M/253176/01/2, SA04191, M/253176/01/2/OCR. Unpublished.
48023840	McElligott, A. (2005) BYF 14182 - Preliminary 28-Day Toxicity Study in the Dog by Dietary Administration: Final Report. Project Number: M/256713/01/2, SA04300, M/256713/01/2/OCR. Unpublished
48024009	Odin-Feurtet, M. (2009) BYF 14182 (FS 240) - *In Vivo* Dermal Absorption Study in the Male Rat. Project Number: M/357205/01/2/OCR, SA/08325, M/357205/01/2. Unpublished
Memo	Brunsman, L. 2011. Penflufen Qualitative Risk Assessment Based on Wistar Rat Dietary Study. 1/27/11. TXR No. 0055636.

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